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pregnancy. Furthermore, lovastatin can arrest cells in the G-1 phase of the cell cycle.<sup>5</sup> Dietary intervention and the use of bile-acid sequestrants may not lower cholesterol concentrations sufficiently during pregnancy and may result in micronutrient inadequacy harmful to fetal growth. Dietary manipulation may require supplementation with vitamins and minerals. All these measures may best be left until after the birth. Equally important is the population or public-health approach to risk prevention in children and young adults before they themselves become parents.<sup>6</sup>

Data from the Bogalusa Heart Study and other populations of children in the USA suggest a high prevalence of obesity and of adverse serum lipid concentrations and blood pressure values among children. The presence of a family history of heart disease, more than one risk factor for CHD in childhood, and adverse behaviours, such as excess dietary intake of calories, saturated fat and cholesterol, cigarette smoking, and physical inactivity, are harbingers of the development of cardiovascular disease. Cardiovascular risk factors do not occur as isolated events. They persist into adulthood, resulting in progressive target-organ damage from both atherosclerosis and hypertension, even in early life. Since unfavourable lifestyles and related traits, such as raised blood pressure and serum lipids and early atherosclerosis, are so prevalent among people in industrialised countries, it is imperative to examine all children and start prevention early in life.

The Finnish experience (STRIP Study) has shown that lowering of dietary fat in infancy does not harm growth during the first 3 years of life.<sup>7</sup> Nor did the Dietary Intervention Study in Children (DISC) show adverse effects of lowering of dietary fat on growth among preadolescents.<sup>8</sup> In terms of drug therapy for familial hypercholesterolaemia, a study of the efficacy and safety of lovastatin among adolescent boys with familial hypercholesterolaemia showed no adverse effects on growth and sexual development over the 48-week duration of the trial.<sup>9</sup> It would be prudent to consider drug therapy for children at very high risk of atherosclerosis after completion of pubertal growth, especially for those with LDL cholesterol above 160 mg/dL (4.1 mmol/L) despite rigid dietary treatment and a positive family history of CHD and hypercholesterolaemia.

Findings from the paediatric studies cited above, complemented by necropsy data,<sup>1-3</sup> show clearly that risk factors can be identified in childhood, and that dietary manipulation to decrease intake of saturated fat and cholesterol without undue restriction of calories has not interfered with growth. The increasing secular trends in obesity, the spread of cardiovascular disease worldwide, and the increasing prevalence of type 2 diabetes are compelling reasons for attempts to alter the natural course of atherosclerosis to start in childhood.

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## Should all pregnant women be screened for hypothyroidism?

Screening of all pregnant women for hypothyroidism, preferably in the first trimester, has been proposed by researchers whose large-scale retrospective study showed that mild or subclinical maternal hypothyroidism during pregnancy is associated with the child's poor performance on neuropsychological tests.<sup>1</sup> This proposal has been endorsed by the Endocrine Society in the USA, which has called for the development of a cost-effective screening programme of pregnant women for hypothyroidism (<http://www.endo-society.org/maternalthyroiddeficiency> [accessed on Oct 4, 1999]).

The findings by James Haddow and colleagues<sup>1</sup> are important in emphasising the susceptibility of the developing brain to thyroid disturbances during gestation. There is evidence that the developing human brain needs thyroid hormone from the first trimester of gestation,<sup>2</sup> and until the fetal thyroid starts to produce thyroxine in midgestation, the fetus obtains its hormone entirely from the mother. Maternal serum concentrations of free thyroxine (FT4) at or below the tenth percentile at 12 weeks' gestation (but not at 32 weeks) are associated with delayed psychomotor development at age 10 months.<sup>3</sup> This finding—that maternal FT4 concentrations at the lower end of the normal range at the end of the first trimester result in an insufficient placental transfer of thyroxine—indicates that the risk of impaired neurodevelopment due to low exposure to the hormone is not confined to children of mothers with thyroid disease. However, is there sufficient evidence that screening of pregnant women for thyroid function, followed by treatment of those with mild hypothyroidism, will provide worthwhile benefit to the children?<sup>1,4</sup>

In Haddow and colleagues' study, 15 tests relating to intelligence, attention, school performance, and visual motor skills were given to 62 children aged 7-9 years whose mothers' serum collected during pregnancy indicated hypothyroidism. There was a significant 4-point difference between the groups in mean IQ, but this difference represents only a small effect size.<sup>5</sup> More important than the overall group difference, though, is whether there is a difference in proportions of children with low IQ scores. In the general population, about 16% of children have IQs that are more than 1 SD (15 points) below the mean (ie, IQs lower than 85).<sup>3</sup> A similar percentage (15%) was found among the children of the hypothyroid women in Haddow and colleagues' study so, although this proportion is significantly greater than the 5% found among the controls,

the difference might be due to high performance among the controls rather than poor functioning among the cases.

Another point to consider is that the effects of thyroxine deficiency or thyroxine supplementation may differ for various neurodevelopmental features. For example, Haddow and colleagues' findings indicate that attention is adversely affected among children of women treated for hypothyroidism.<sup>1</sup> In another study,<sup>6</sup> cognitive development was appropriate among children with congenital hypothyroidism given thyroxine supplements early, but when the children were examined according to hormone concentrations, attention deficits and subtle motor problems were commoner among those with the highest FT4 concentrations, although these concentrations were within the normal range.<sup>4</sup> Such findings suggest that treatment with thyroxine might not be free of adverse effects, and this point must be clarified before a decision to screen is taken.

Once the benefit of screening is decided upon, its practicability and its sensitivity and specificity should also be considered, as the Endocrine Society plans to do. For instance, what variable should be used for the screening? Should it be thyrotropin, FT4, or thyroid peroxidase antibody (TPO-Ab)? Generally, the detection of thyroid dysfunction is based initially on thyrotropin concentration, and the society has recommended that for now this hormone should be measured for women with personal or family history of thyroid disease or symptoms suggestive of hypothyroidism. But how accurate is thyrotropin as an index of maternal FT4 concentrations or of adequacy of thyroxine transfer to the fetus? Low concentrations of maternal serum FT4 have been associated with normal thyrotropin concentrations during pregnancy, and this pattern has been termed gestational hypothyroxinaemia, a state in which the "thyroxine environment" is inappropriate for the fetus rather than for the mother.<sup>7</sup> If FT4 is the variable to be used in screening, what cut-off value should be used to define gestational hypothyroxinaemia? Informed choice would require knowledge of the frequency distribution of FT4 concentrations in iodine-replete women (probably for each trimester of pregnancy).<sup>7</sup> The predictive power of TPO-Ab is too low for use in screening, even though women with these antibodies are at increased risk of having FT4 concentrations at the low end of the normal range at 12 weeks' gestation.<sup>1,3</sup>

The next question to consider is when the woman should be screened. The first antenatal visit, even if it is in the first trimester, might be too late. The logistics of preconception screening are enormous. Besides, the relation between maternal FT4 concentrations before pregnancy and those during early pregnancy is not known.

Finally, how should the mother be treated? The relation between low maternal FT4 and impairment of the child's neurodevelopment has not been proven to be causal. The recent identification of metabolic pathways other than transplacental diffusion involved in maternal-fetal transfer of FT4<sup>8</sup> might mean that low concentrations of maternal thyroid hormone only indirectly impair the supply of thyroid hormone to the fetus. The possibility that children at risk would benefit from treatment of the mother with thyroxine should be confirmed by a placebo-controlled trial of adequate statistical power, after the dose and the duration of supplementation of thyroxine have been studied in greater detail.

Finally, is there an alternative to screening followed by therapy? As pointed out in the commentary accompanying

Haddow and colleagues' paper,<sup>9</sup> even in areas where the environment contains sufficient iodine, public-health measures to encourage adequate iodine intake, which should be increased during pregnancy, should not be forgotten. Such measures are easier to implement than screening of thyroid function during or before pregnancy, and will benefit the general population.

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## A stimulating new target for cancer immunotherapy

The past few years have seen a striking expansion in knowledge about the signals and switches involved in cellular immunity. CD40 has emerged as a particularly important molecule, and its central role is starting to be exploited in studies of immunotherapy for tumours in human beings. Three recent papers<sup>1-3</sup> suggest that antibodies to CD40 can stimulate (not block) CD40 and provoke immunity to tumours in mice.

CD40 induces immunity through activation and expansion of dendritic cells, B cells, and T cells. CD40 was originally identified as an activator of B-lymphocyte proliferation and is a transmembrane protein of the family of tumour-necrosis-factor receptors. Interaction between CD40 on dendritic cells and the CD40 ligand (CD40L, now designated CD154) on naïve CD4-positive T-helper cells plays a crucial role at the start of the immune response, in which the T-helper cells undergo activation and the dendritic cells mature. Signalling through CD40 on dendritic cells enables them to present antigen more effectively, through expression of costimulatory molecules and the production of interleukin-12, which in turn produces further T-cell stimulation. The activated T-helper cells can then signal to B cells via CD40,<sup>4</sup> so that CD40-activated B cells also develop a potent antigen-presenting function.<sup>5</sup> CD40-activated antigen-presenting cells can in their turn stimulate CD8-positive cytotoxic T cells.<sup>6,7</sup> These interactions explain how rare T-helper and cytotoxic T cells with receptors specific for a particular antigen (eg, a tumour antigen) can both be stimulated by the same antigen-presenting cell without all three being present simultaneously. Activated T-helper cells can stimulate